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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
MYERS, CARLA J

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 07/02/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/674,607	PRASHAR ET AL.	
	Examiner	Art Unit	
	Carla Myers	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 April 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *21 and 34-46* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *21 and 34-46* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election of Group VI in the response of January 5, 2004 and of the species of the disease glomerulonephritis, the cell of peripheral T lymphocytes and the expression profile comprising each of SEQ ID NO: 1-34 in the response of April 21, 2004 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Priority

2. The first line of the specification indicates that the present application is "based on" application 60/084,329. It appears that Applicant's intend to claim the benefit of a prior filed provisional application under 35 U.S.C. 119(e). However, copendency between the current application and the prior provisional application is required. Accordingly, the first page of the specification should be updated to indicate that the present application is the National Stage of International Application PCT/US99/09761, filed May 5, 1999, which claims the benefit of U.S. Provisional Application 60/084,329, filed May 5, 1998.

The first paragraph of the specification also indicates that the present application is "related to" applications 08/510,032, 08/688,514, 60/056,844 and 60/056,861. The specification does not state a clear relationship between these applications and the present application (e.g., a continuation-in-part of a nonprovisional U.S. application, etc) and priority to these applications is not set

forth in the Oath/Declaration. Accordingly, priority to these applications has not been granted.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 21 and 34-46 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are drawn to methods for diagnosing a disorder in a subject wherein the methods comprise providing a gene expression profile of a T-lymphocyte population from a subject and comparing this gene expression profile to a second T lymphocyte gene expression profile from a subject having a disorder and to a third gene expression profile from a normal T-lymphocyte population and determining if the subject has the disorder. In particular, the disorder is the inflammatory disease glomerulonephritis, the T lymphocyte population comprises peripheral T lymphocytes and the expression profile comprises SEQ ID NO: 1-34.

The specification exemplifies methods of generating expression profiles from T lymphocyte cells and methods of comparing gene expression profiles from treated and untreated populations of T lymphocytes. The specification (see

Example 5 and Figure 4) teaches 16 sequences that are upregulated or downregulated in activated Jurkat cells as compared to quiescent Jurkat cells. In Figure 5, SEQ ID NO:14-33 are disclosed as being differentially expressed in activated versus quiescent T lymphocytes. The specification outlines the steps that one could perform to compare the gene expression patterns of T lymphocytes MPCs from undiagnosed patients to the gene expression patterns of normal T lymphocytes and T lymphocytes obtained from subjects having a disorder such as glomerulonephritis (pages 47-48). It is stated that "(t)he expression profile prepared from the subject can then be compared to the expression profiles prepared from T lymphocytes isolated from patients with various inflammatory disorders…to determine which expression profile most closely matches the expression profile prepared from the patient, thereby, diagnosing whether the patient has a sterile inflammatory disease, immunodeficiency disorder or autoimmune disorder."

However, the specification has not provided sufficient guidance to enable the skilled artisan to diagnose a disorder by comparing the expression pattern of T lymphocytes from a subject to the expression profile of T lymphocytes from reference normal or glomerulonephritis disease states or from other disease states. The specification does not provide any specific gene profiles that conclusively represent a normal or glomerulonephritis or other type of disease state. The claims as broadly written encompass analyzing the expression profile of any gene or combination of genes. Thereby, the claims encompass analyzing a significantly large number of nucleic acids to determine which of the nucleic

acids have an expression pattern specifically correlated with glomerulonephritis or another type of disease. Even if the claims were amended to reflect the elected invention of the combination of sequences of SEQ ID NO: 1-34, the specification has not establish that any one of these sequences or combinations of sequences is associated with a particular disease state. While the specification has shown that the expression of fragments of nucleic acid vary in activated and quiescent T lymphocytes, the specification has not establish that the expression pattern of the nucleic acid fragments vary between normal and disease states. Accordingly, to practice the claimed invention, one must first determine an expression profile that is generally characteristic of a normal T lymphocyte (specifically a peripheral T lymphocyte) and an expression profile that is specifically characteristic of T lymphocytes from individual's having sterile inflammatory disorders, autoimmune disorders, immunodeficiency disorders, cancer and/or GVHD (specifically the disorder glomerulonephritis). Such experimentation is considered undue. While the techniques for creating gene expression profiles are known in the art, the results of performing such methods as they relate to normal and diseased T lymphocytes are not known and are unpredictable. Specifically, it is unpredictable as to what would constitute a normal T lymphocyte gene expression profile and what would constitute a T lymphocyte gene expression profile characteristic of sterile inflammatory disorders, autoimmune disorders, immunodeficiency disorders, cancer or GVHD, or characteristic of glomerulonephritis. The specification does not provide any working examples of diagnosing a disease state by comparing the T lymphocyte

gene expression profile of a patient to that of a reference normal or disease state. Extensive experimentation would be required to obtain gene expression profiles that specifically represent the normal state of T lymphocytes and disease state of T lymphocytes and which could be used to diagnose a disease state in the general population. Additionally, the specification does not provide sufficient guidance as to how to evaluate the results of the comparison step and as to how to determine whether a gene profile "most closely matches" a disease or control state in order to allow for a diagnosis of a disease state. The specification does not teach any particular genes that are up-regulated or down-regulated in T lymphocytes from patients having a disorder as compared to T lymphocytes from normal subjects. There are also no teachings in the specification as to the number of genes that must be commonly up-regulated or down-regulated in order to diagnose a disease state. Similarly, the specification does not teach if any particular class or member of a class of genes must be analyzed to allow for the diagnosis of a disease state. Of the sequences set forth in Figures 4 and 5, 21 appear to be of unknown function (i.e. do not "match" any known human gene sequence). Additionally, these sequences appear to represent small fragments of gene sequences. There are no teachings in the specification as to whether the gene fragments are specific for a single gene or cross hybridize with additional genes, that may or may not be expressed in T lymphocytes from different disease states. It is unclear as to which of the sequences disclosed in the specification are up-regulated or down-regulated in sterile inflammatory disorders, autoimmune disorders, immunodeficiency disorders, cancer or GVHD,

or and which of the sequences could be used to diagnose a disease state such as glomerulonephritis.

Case law has established that "(t)o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.'" *In re Wright* 990 F.2d 1557, 1561. *In re Fisher,* 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) it was determined that "(t)he scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art". The amount of guidance needed to enable the invention is related to the amount of knowledge in the art as well as the predictability in the art Furthermore, the Court in *Genetech Inc. v Novo Nordisk* 42 USPQ2d 1001 held that "(I)t is the specification, not the knowledge of one skilled in the art that must supply the novel aspects of the invention in order to constitute adequate enablement". In the instant case, the state of the art of identifying specific gene expression patterns associated with particular disease states is highly unpredictable. There is no predictable means for determining which nucleic acids combination of nucleic acids are specifically up-regulated or down-regulated in diseased versus normal cells. Such information can only be obtained through extensive experimentation. Additionally, the specification does not provide sufficient guidance as to how to interpret the results of methods which compare gene expression profiles and does not adequately teach how one determines if a gene expression profile is sufficiently similar so as to allow for the diagnosis of a disease. Further, the specification does not teach the "novel

aspects of the invention." That is, the specification does not teach any particular genes or gene expression profiles that are characteristic of normal or diseased T lymphocytes. The specification does not provide any reasonable expectation that one could obtain a gene expression profile specific for glomerulonopephritis or other disorder without undue experimentation. Accordingly, in view of the lack of specific guidance and disclosure provided in the specification, undue experimentation would be required to practice the claimed invention.

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 21 and 34-46 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 21 and 34-46 are indefinite. The claims are drawn to methods for diagnosing a disease and include the step of comparing an expression profile from a subject to an expression profile from a T lymphocyte population from a subject having a disease and to an expression profile from a normal T lymphocyte population. Following the comparing step, the claim includes a limitation of determining if the subject has a sterile inflammatory disease, autoimmune disorder, immunodeficiency disease, cancer, or GVHD. However, the claim does not clearly set forth the relationship between the comparing and determining step and does not clearly indicate how the comparison step results in the determination of whether the subject has a sterile inflammatory disease, autoimmune disorder, immunodeficiency disease, cancer, or GVHD.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 21, 34, 35, 44-46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rohrer et al (U.S. Patent No. 6,335,174).

Rohrer (columns 11-12) teaches methods for screening an individual for early stage carcinoma or lymphoma wherein the methods comprise analyzing a T cell population for the presence of mRNAs encoding the cytokines IL-2, IFN-γ, IL-4 and IL-10. Rohrer teaches that the mRNA expression levels of these cytokines are correlated with the occurrence and progression of cancer. Rohrer does specifically exemplify a method that includes the step of comparing the

expression profile of the subject to that a control T cell population and a T cell population obtained from a subject having cancer. However, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Rohrer so as to have compared the T lymphocyte mRNA levels of IL-2, IFN-γ, IL-4 and IL-10 of a test subject to the T lymphocyte mRNA levels of IL-2, IFN-γ, IL-4 and IL-10 from a control subject and a subject having cancer in order to have included a positive and negative control in the assay which thereby would have provided a more accurate and effective means for screening for cancer.

7. Claims 42 and 43 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rohrer et al (U.S. Patent No. 6,335,174) in view of Chee (cited in the IDS).

The teachings of Rohrer are presented above. Rohrer teaches using probes to IL-2, IFN-γ, IL-4 and IL-10 to assay for mRNA expression. Rohrer does not teach assaying for gene expression by measuring hybridization between sample nucleic acid molecules and nucleic acid molecules immobilized onto a solid support.

However, Chee (see, for example, abstract and page 610) teaches methods for assaying for gene expression wherein the methods comprise immobilizing probes onto a solid support and hybridizing the probes with a sample of nucleic acids. The solid supports of Chee allow for effective and simultaneous analysis of large numbers of nucleic acids.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have immobilized the probes of Rohrer

onto a solid support as taught by Chee in order to have provided a simple and effective means for simultaneously analyzing mRNAs associated with the occurrence of cancer.

8. The prior art does not teach or suggest the elected embodiment of a method for diagnosing glomerulonephritis wherein the method comprises comparing a gene expression profile obtained from peripheral T lymphocytes of a subject to a second gene expression profile obtained from normal peripheral T lymphocytes and to a third gene expression profile obtained from peripheral T lymphocytes of a subject having glomerulonephritis, wherein the gene expression profile consists of the nucleic acids of SEQ ID NO: 1-34.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carla Myers whose telephone number is (571) 272-0747. The examiner can normally be reached on Monday-Thursday from 6:30 AM-5:00 PM. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion, can be reached on (571)-272-0782.

Papers related to this application may be faxed to Group 1634 via the PTO Fax Center using the fax number (703)-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Carla Myers
June 21, 2004

CARLA J. MYERS
PRIMARY EXAMINER